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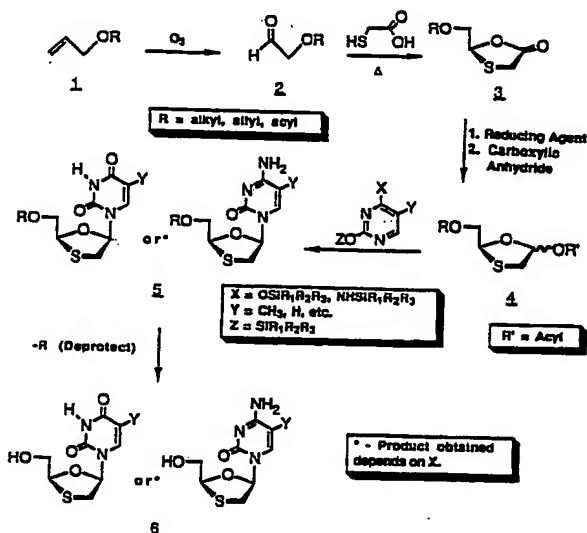
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(54) Title: METHOD AND COMPOSITIONS FOR THE SYNTHESIS OF BCH-189 AND RELATED COMPOUNDS



(57) Abstract

The present invention relates to a method of preparing BCH-189 and various analogs of BCH-189 from inexpensive precursors with the option of introducing functionality as needed. This synthetic route allows the stereoselective preparation of the biologically active isomer of these compounds, β -BCH-189 and related compounds. Furthermore, the stereochemistry at the nucleoside 4' position can be controlled to produce enantiomerically-enriched β -BCH-189 and its analogs.

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METHOD AND COMPOSITIONS FOR THE SYNTHESIS OF BCH-189
AND RELATED COMPOUNDS

TECHNICAL FIELD

5

The present invention relates to methods and compositions for preparing antiviral nucleoside analogs, particularly BCH-189 (2',3'-dideoxy-3'-thia-cytidine). More particularly, the invention relates to the selective
10 synthesis of the β -isomer of BCH-189 and related compounds as well as the selective synthesis of enantiomerically-enriched BCH-189 and related compounds.

BACKGROUND ART

15

In 1981, documentation began on the disease that became known as Acquired Immune Deficiency Syndrome (AIDS), as well as its forerunner AIDS Related Complex (ARC). In 1983, the cause of the disease AIDS was established as a virus named the Human Immunodeficiency
20 Virus type 1 (HIV-1). Usually, a person infected with the virus will eventually develop AIDS; in all known cases of AIDS the final outcome has always been death.

25

The disease AIDS is the end result of an HIV-1 virus following its own complex life cycle. The virion life cycle begins with the virion attaching itself to the host human T-4 lymphocyte immune cell through the bonding of a glycoprotein on the surface of the virion's protective coat with the CD4 glycoprotein on the
30 lymphocyte cell. Once attached, the virion sheds its glycoprotein coat, penetrates into the membrane of the host cell, and uncoats its RNA. The virion enzyme, reverse transcriptase, directs the process of transcribing the RNA into single stranded DNA. The viral RNA is
35 degraded and a second DNA strand is created. The now double-stranded DNA is integrated into the human cell's genes and those genes are used for cell reproduction.

At this point, the human cell carries out its reproductive process by using its own RNA polymerase to transcribe the integrated DNA into viral RNA. The viral RNA is translated into glycoproteins, structural proteins, and viral enzymes, which assemble with the viral RNA intact. When the host cell finishes the reproductive step, a new virion cell, not a T-4 lymphocyte, buds forth. The number of HIV-1 virus cells thus grows while the number of T-4 lymphocytes decline.

10

The typical human immune system response, killing the invading virion, is taxed because a large portion of the virion's life cycle is spent in a latent state within the immune cell. In addition, viral reverse transcriptase, the enzyme used in making a new virion cell, is not very specific, and causes transcription mistakes that result in continually changed glycoproteins on the surface of the viral protective coat. This lack of specificity decreases the immune system's effectiveness because antibodies specifically produced against one glycoprotein may be useless against another, hence reducing the number of antibodies available to fight the virus. The virus continues to grow while the immune response system continues to weaken. Eventually, the HIV largely holds free reign over the body's immune system, allowing opportunistic infections to set in and ensuring that, without the administration of antiviral agents and/or immunomodulators, death will result.

20

There are three critical points in the virus's life cycle which have been identified as targets for antiviral drugs: (1) the initial attachment of the virion to the T-4 lymphocyte, or macrophage, site, (2) the transcription of viral RNA to viral DNA, and (3) the assemblage of the new virion cell during reproduction.

30

Inhibition of the virus at the second critical point, the viral RNA to viral DNA transcription process, has provided the bulk of the therapies used in treating AIDS. This transcription must occur for the virion to
5 reproduce because the virion's genes are encoded in RNA; the host cell reads only DNA. By introducing drugs that block the reverse transcriptase from completing the formation of viral DNA, HIV-1 replication can be stopped.

10 Nucleoside analogs, such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxycytidine (DDC), 2',3'-dideoxythymidinene (D4T), 2',3'-dideoxyinosine (DDI), and various fluoro-derivatives of these nucleosides are relatively effective in halting HIV replication at the
15 reverse transcriptase stage. Another promising reverse transcriptase inhibitor is 2',3'-dideoxy-3'-thia-cytidine (BCH-189), which contains an oxathiolane ring substituting for the sugar moiety in the nucleoside.

20 AZT is a successful anti-HIV drug because it sabotages the formation of viral DNA inside the host T-4 lymphocyte cell. When AZT enters the cell, cellular kinases activate AZT by phosphorylation to AZT triphosphate. AZT triphosphate then competes with natural
25 thymidine nucleosides for the receptor site of HIV reverse transcriptase enzyme. The natural nucleoside possesses two reactive ends, the first for attachment to the previous nucleoside and the second for linking to the next nucleoside. The AZT molecule has only the first reactive
30 end; once inside the HIV enzyme site, the AZT azide group terminates viral DNA formation because the azide cannot make the 3',5'-phosphodiester with the ribose moiety of the following nucleoside.

35 AZT's clinical benefits include increased longevity, reduced frequency and severity of opportunistic infections, and increased peripheral CD4 lymphocyte count.

Immunosorbent assays for viral p24, an antigen used to track HIV-1 activity, show a significant decrease with use of AZT. However, AZT's benefits must be weighed against the severe adverse reactions of bone marrow suppression, 5 nausea, myalgia, insomnia, severe headaches, anemia, peripheral neuropathy, and seizures. Furthermore, these adverse side effects occur immediately after treatment begins whereas a minimum of six weeks of therapy is necessary to realize AZT's benefits.

10

Both DDC and D4T are potent inhibitors of HIV replication with activities comparable (D4T) or superior (DDC) to AZT. However, both DDC and D4T are converted to their 5' triphosphates less efficiently than their natural 15 analogs and are resistant to deaminases and phosphorylases. Clinically, both compounds are toxic. Currently, DDI is used in conjunction with AZT to treat AIDS. However, DDI's side effects include sporadic pancreatitis and peripheral neuropathy. Initial tests on 20 3'-fluoro-2'-3'-dideoxythymidine show that its anti-viral activity is comparable to that of AZT.

Recent tests on BCH-189 have shown that it possesses anti-HIV activity similar to AZT and DDC, but 25 without the cell toxicity which causes the debilitating side effects of AZT and DDC. A sufficient quantity of BCH-189 is needed to allow clinical testing and treatment using the drug.

30

The commonly-used chemical approaches for synthesizing nucleosides or nucleoside analogs can be classified into two broad categories: (1) those which modify intact nucleosides by altering the carbohydrate, the base, or both and (2) those which modify carbohydrates and 35 incorporate the base, or its synthetic precursor, at a suitable stage in the synthesis. Because BCH-189 substitutes a sulfur atom for a carbon atom in the

carbohydrate ring, the second approach is more feasible. The most important factor in this latter strategy involves delivering the base from the β -face of the carbohydrate ring in the glycosylation reaction because only the β -isomers exhibit useful biological activity.

It is well known in the art that the stereoselective introduction of bases to the anomeric centers of carbohydrates can be controlled by capitalizing on the neighboring group participation of a 2-substituent on the carbohydrate ring (Chem. Ber. 114:1234 (1981)). However, BCH-189 and its analogs do not possess a 2-substituent and, therefore, cannot utilize this procedure unless additional steps to introduce a functional group that is both directing and disposable are incorporated into the synthesis. These added steps would lower the overall efficiency of the synthesis.

It is also well known in the art that "considerable amounts of the undesired α -nucleosides are always formed during the synthesis of 2'-deoxyribosides" (Chem. Ber. 114:1234, 1244 (1981)). Furthermore, this reference teaches that the use of simple Friedel-Crafts catalysts like SnCl_4 in nucleoside syntheses produces undesirable emulsions upon the workup of the reaction mixture, generates complex mixtures of the α and β -isomers, and leads to stable σ -complexes between the SnCl_4 and the more basic silylated heterocycles such as silylated cytosine. These complexes lead to longer reaction times, lower yields, and production of the undesired unnatural N-3-nucleosides. Thus, the prior art teaches the use of trimethylsilyl triflate or trimethylsilyl perchlorate as a catalyst during the coupling of pyrimidine bases with a carbohydrate ring to achieve high yields of the biologically active β -isomers. However, the use of these catalysts to synthesize BCH-189 or BCH-189 analogs does

not produce the β -isomer preferentially; these reactions result in approximately a 50:50 ratio of the isomers.

Thus, there exists a need for an efficient synthetic route to BCH-189 and its analogs. There also exists a need for a stereoselective synthetic route to the biologically active isomer of these compounds, β -BCH-189 and related β -analogs. Furthermore, there exists a need for a stereoselective synthetic route to enantiomerically-enriched β -BCH-189 because the other enantiomer is inactive and, therefore, represents a 50% impurity.

DISCLOSURE OF INVENTION

The present invention relates to the discovery of a surprisingly efficient synthetic route to BCH-189 and various analogs of BCH-189 from inexpensive precursors with the option of introducing functionality as needed. This synthetic route allows the stereoselective preparation of the biologically active isomer of these compounds, β -BCH-189 and related compounds. Furthermore, the stereochemistry at the nucleoside 4' position can be controlled to produce enantiomerically-enriched β -BCH-189 and its analogs.

The term "BCH-189 analogs" is meant to refer to nucleosides that are formed from pyrimidine bases substituted at the 5 position that are coupled to substituted 1,3-oxathiolanes.

The method of the present invention includes ozonizing an allyl ether or ester having the formula $\text{CH}_2=\text{CH}-\text{CH}_2-\text{OR}$, in which R is a protecting group, such as an alkyl, silyl, or acyl group, to form a glycoaldehyde having the formula $\text{OHC}-\text{CH}_2-\text{OR}$; adding thioglycolic acid to the glycoaldehyde to form a lactone of the formula 2-(R-oxy)-methyl-5-oxo-1,3-oxathiolane; converting the lactone

to its corresponding carboxylate at the 5 position of the oxathiolane ring; coupling the acetate with a silylated pyrimidine base in the presence of SnCl_4 to form the β -isomer of a 5'-(R-oxy)-2',3'-dideoxy-3'-thia- nucleoside analog; and replacing the R protecting group with a hydrogen to form BCH-189 or an analog of BCH-189.

The invention can be used to produce BCH-189 or BCH-189 analogs that are enantiomerically-enriched at the 4' position by selecting an appropriate R protecting group to allow stereoselective selection by an enzyme. For instance, the R protecting group can be chosen such that the substituent at the 2 position of the oxathiolane lactone is butyryloxy to permit stereoselective enzymatic hydrolysis by pig liver esterase. The resulting optically active hydrolyzed lactone can then be converted to its corresponding diacetate and coupled with a silylated pyrimidine base as above.

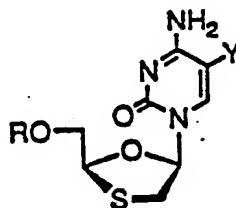
Accordingly, one of the objectives of this invention is to provide an efficient method for preparing the β -isomer of BCH-189 and analogs of BCH-189 in high yields. Furthermore, it is an objective of this invention to provide a synthetic method to produce only one optical isomer, rather than a racemic mixture, of BCH-189 and analogs of BCH-189. A further object of this invention is to provide a synthetic route to produce β -BCH-189 that is enantiomerically-enriched.

Additionally, an objective of this invention is to provide intermediates from which BCH-189 or BCH-189 analogs can be synthesized of the formula 2-(R-oxymethyl)-5-acyloxy-1,3-oxathiolane, wherein R is a protecting group, such as alkyl, silyl, or acyl, and a method of preparing these compounds. Furthermore, it is an object of this invention to provide enantiomerically-enriched 2-acetoxymethyl-5-acetoxy-1,3-oxathiolane and 2-

butoxymethyl-5-oxo-1,3-oxathiolane and methods of preparing these compounds.

Another objective of this invention is to provide intermediates from which BCH-189 or BCH-189 analogs can be synthesized of the formula:

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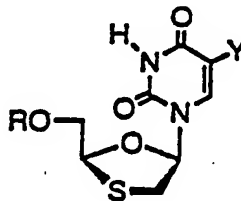


wherein R is a protecting group, such as alkyl, silyl, or acyl, and Y can be hydrogen, methyl, halo, alkyl, alkenyl, alkynyl, hydroxalkyl, carboxalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and selenoaryl, and methods of preparing these compounds.

20

Furthermore, this invention provides intermediates from which BCH-189 or BCH-189 analogs can be synthesized of the formula:

25



wherein R is a protecting group, such as alkyl, silyl, or acyl, and Y can be hydrogen, methyl, halo, alkyl, alkenyl, alkynyl, hydroxalkyl, carboxalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and selenoaryl, and methods of preparing these compounds.

35

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates one embodiment of a synthesis of BCH-189 and BCH-189 analogs according to the present invention;

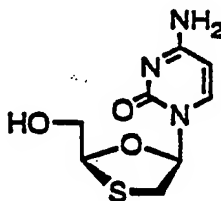
Figure 2 illustrates one embodiment of the synthesis of BCH-189 according to the present invention;

Figure 3 illustrates one embodiment of the synthesis of 5-methylcytidine and thymidine derivatives of BCH-189 according to the present invention; and

Figure 4 illustrates one embodiment of the synthesis of enantiomerically-enriched BCH-189 according to the present invention.

BEST MODE OF CARRYING OUT THE INVENTION

BCH-189 is a compound of the formula:



The process of the present invention for preparing BCH-189 and BCH-189 analogs is set forth in Fig. 1. An allyl ether or ester 1 is ozonized to give an aldehyde 2, which reacts with thioglycolic acid to give a lactone 3. The lactone 3 is treated with a reducing agent, followed by a carboxylic anhydride, to produce the carboxylate 4. This carboxylate is coupled with a silylated pyrimidine base in the presence of a Lewis acid that can catalyze stereospecific coupling, such as SnCl₄, to yield the β -isomer of the substituted nucleoside 5 in essentially a 100:0 ratio of β : α isomers. The substituted

nucleoside 5 is deprotected to produce BCH-189 or BCH-189 analog 6.

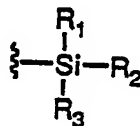
This procedure can be tailored to produce BCH-189 or BCH-189 analogs that are enantiomerically-enriched at the 4' position by selecting an appropriate R protecting group to allow stereoselective enzymatic hydrolysis of 3 by an enzyme such as pig liver esterase, porcine pancreatic lipase, or subtilisin or other enzymes that hydrolyze 3 in a stereoselective fashion. The resulting optically active 3 can be converted to enantiomerically-enriched carboxylate 4 and coupled with a silylated pyrimidine base as above to produce enantiomerically-enriched BCH-189 or BCH-189 analogs.

15

The protecting group R in 1 can be selected to provide protection for the corresponding alcohol until the final step in the synthesis is carried out (deprotection of 5 to form 6). Additionally, the protecting group can be selected, if desired, to provide an additional recognition site for an enzyme to be used later in an enantio-selective hydrolysis reaction. Any group that functions in this manner may be used. For instance, alkyl, silyl, and acyl protecting groups or groups that possess substantially the same properties as these groups can be used.

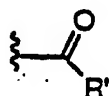
An alkyl protecting group, as used herein, means triphenylmethyl or an alkyl group that possesses substantially the same protecting properties as triphenylmethyl. A silyl protecting group, as used herein, means a trialkylsilyl group having the formula:

35



wherein R_1 , R_2 , and R_3 may be lower-alkyl, e.g., methyl, ethyl, butyl, and alkyl possessing 5 carbon atoms or less; or phenyl. Furthermore, R_1 may be identical to R_2 ; R_1 , R_2 , and R_3 may all be identical. Examples of silyl protecting groups include, but are not limited to, trimethylsilyl and t-butyldiphenylsilyl.

An acyl group, as used herein to describe an acyl protecting group (as in 1) or to describe a carboxylate (as in 4), is a group having the formula:

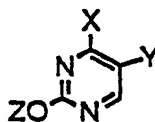


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wherein R' is a lower alkyl, e.g., methyl, ethyl, butyl, and alkyl possessing 5 carbon atoms or less; substituted lower alkyl wherein the alkyl bears one, two, or more simple substituents, including, but not limited to, amino, carboxyl, hydroxy, phenyl, lower-alkoxy, e.g., methoxy and ethoxy; phenyl; substituted phenyl wherein the phenyl bears one, two, or more simple substituents, including, but not limited to, lower alkyl, halo, e.g., chloro and bromo, sulfato, sulfonyloxy, carboxyl, carbo-lower-alkoxy, e.g., carbomethoxy and carbethoxy, amino, mono- and di-lower alkylamino, e.g., methylamino, amido, hydroxy, lower alkoxy, e.g., methoxy and ethoxy, lower-alkanoyloxy, e.g., acetoxy.

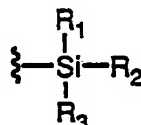
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A silylated pyrimidine base, as used herein, means a compound having the formula:



35

wherein X is either a trialkylsilyloxy or a trialkylsilylamino group, Z is a trialkylsilyl group, and Y is further described below. A trialkylsilyl group, as used herein, means a group having the formula:



10

wherein R_1 , R_2 , and R_3 may be lower-alkyl, e.g., methyl, ethyl, butyl, and alkyl possessing 5 carbon atoms or less, or phenyl. Furthermore, R_1 may be identical to R_2 ; R_1 , R_2 , and R_3 may all be identical. Examples of trialkylsilyl groups include, but are not limited to, trimethylsilyl and t-butyl-diphenylsilyl.

The silylated pyrimidine base may be substituted with various Y substituents, including, but not limited to, hydrogen, methyl, halo, alkyl, alkenyl, alkynyl, hydroxyalkyl, carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and selenoaryl, at position 5 of the silylated pyrimidine base (Y substituent in Fig. 1) to modify the properties, such as transport properties or the rate of metabolism, of the BCH-189 analog.

Illustrative examples of the synthesis of BCH-189 or BCH-189 analogs according to the present invention are given in Figs. 2, 3, and 4 and the following descriptions.

Figure 2 shows the synthesis of BCH-189 starting with allyl alcohol 7. A NaH oil suspension (4.5 g, 60%, 110 mmol) was washed with THF twice (100 ml x 2) and the resulting solid suspended in THF (300 ml). The suspension was cooled to 0°C, allyl alcohol 7 (6.8 ml, 100 mmol) was

added dropwise, and the mixture was stirred for 30 minutes at 0°C. t-Butyl-diphenylsilyl chloride (25.8 ml, 100.8 mmol) was added dropwise at 0°C and the reaction mixture was stirred for 1 hour at 0°C. The solution was quenched
5 with water (100 ml), and extracted with diethyl ether (200 ml x 2). The combined extracts were washed with water, dried over MgSO₄, filtered, concentrated, and the residue distilled under vacuum (90-100°C at 0.5-0.6 mm Hg) to give a colorless liquid 8 (28 g., 94 mmol, 94%). (¹H NMR: 7.70-
10 7.35 (10H, m, aromatic-H); 5.93 (1H, m, H₂); 5.37 (1H, dt, H₁) J=1.4 and 14.4 Hz; 5.07 (1H, dt, H₁) J=1.4 and 8.7 Hz; 4.21 (2H, m, H₃); 1.07 (9H, s, t-Bu))

The silyl allyl ether 8 (15.5 g, 52.3 mmol) was
15 dissolved in CH₂Cl₂ (400 ml), and ozonized at -78°C. Upon completion of ozonolysis, DMS (15 ml, 204 mmol, 3.9 eq) was added at -78°C and the mixture was warmed to room temperature and stirred overnight. The solution was washed with water (100 ml x 2), dried over MgSO₄, filtered,
20 concentrated, and distilled under vacuum (100-110°C at 0.5-0.6 mm Hg) to give a colorless liquid 9 (15.0 g, 50.3 mmol, 96%). (¹H NMR: 9.74 (1H, s, H-CO); 7.70-7.35 (10H, m, aromatic-H); 4.21 (2H, s, -CH₂); 1.22 (9H, s, t-Bu))

25 Silayted glycoaldehyde 9 (15.0 g, 50.3 mmol) was dissolved in toluene (200 ml) and thioglycolic acid (3.50 ml, 50.3 mmol) was added all at once. The solution was refluxed for 2 hours while the resulting water was removed with a Dean-Stark trap. The solution was cooled to room
30 temperature and washed with saturated NaHCO₃ solution and the aqueous washings were extracted with diethyl ether (200 ml x 2). The combined extracts were washed with water (100 ml x 2), dried over MgSO₄, filtered, and concentrated to give a colorless oil 10 (16.5 g, 44.3
35 mmol, 88%), which gradually solidified under vacuum. Recrystallization from hexane afforded a white solid 10 (15.8 g, 84%). (¹H NMR: 7.72-7.38 (10H, m, aromatic-H);

5.53 (1H, t, H₂) J=2.7 Hz; 3.93 (1H, dd, -CH₂O) J=9.3 Hz;
3.81 (1H, d, 1H₄) J=13.8 Hz; 3.79 (1H, dd, -CH₂O); 3.58
(1H, d, 1H₄); 1.02 (9H, s, t-Bu))

5 2-(t-Butyl-diphenylsilyloxy)-methyl-5-oxo-1,2-
oxathiolane 10 (5.0 g, 13.42 mmol) was dissolved in
toluene (150 ml) and the solution was cooled to -78°C.
Dibal-H solution (14 ml, 1.0 M in hexanes, 14 mmol) was
added dropwise, while the inside temperature was kept
10 below -70°C all the time. After the completion of the
addition, the mixture was stirred for 30 minutes at -78°C.
Acetic anhydride (5 ml, 53 mmol) was added and the mixture
was warmed to room temperature and stirred overnight.
Water (5 ml) was added to the mixture and the resulting
15 mixture was stirred for 1 hour at room temperature. The
mixture was diluted with diethyl ether (300 ml), MgSO₄ (40
g) was added, and the mixture was stirred vigorously for 1
hour at room temperature. The mixture was filtered,
concentrated, and the residue flash chromatographed with
20 20% EtOAc in hexanes to give a colorless liquid 11 (3.60
g, 8.64 mmol, 64%), which was a 6:1 mixture of anomers.
(¹H NMR of the major isomer: 7.70-7.35 (10H, m, aromatic-
H); 6.63 (1H, d, H₅) J=4.4 Hz; 5.47 (1H, t, H₂); 4.20-3.60
(2H, m, -CH₂O); 3.27 (1H, dd, 1H₄) J=4.4 and 11.4 Hz; 3.09
25 (1H, d, 1H₄) J=11.4 Hz; 2.02 (3H, s, CH₃CO); 1.05 (9H, s,
t-Bu); ¹H NMR of the minor isomer: 7.70-7.35 (10H, m,
aromatic-H); 6.55 (1H, d, H₅) J=3.9 Hz; 5.45 (1H, t, H₂);
4.20-3.60 (2H, m, -CH₂O); 3.25 (1H, dd, 1H₄) J=3.9 and 11.4
Hz; 3.11 (1H, d, 1H₄) J=11.4 Hz; 2.04 (3H, s, CH₃CO); 1.04
30 (9H, s, t-Bu))

 2-(t-Butyl-diphenylsilyloxy)-methyl-5-acetoxy-
1,3-oxathiolane 11 (0.28 g, 0.67 mmol) was dissolved in
1,2-dichloroethane (20 ml), and silylated cytosine 12
35 (0.20 g, 0.78 mmol) was added at once at room temperature.
The mixture was stirred for 10 minutes and to it was added
SnCl₄ solution (0.80 ml, 1.0 M solution in CH₂Cl₂, 0.80

mmol) dropwise at room temperature. Additional cytosine 12 (0.10 g, 0.39 mmol) and SnCl_4 solution (0.60 ml) were added in a same manner 1 hour later. After completion of the reaction in 2 hours, the solution was concentrated, and the residue was triturated with triethylamine (2 ml) and subjected to flash chromatography (first with neat EtOAc and then 20% ethanol in EtOAc) to give a tan solid 13 (100% β configuration) (0.25 g, 0.54 mmol, 80%). (^1H NMR ($\text{DMSO}-d_6$): 7.75 (1H, d, H_6) $J=7.5$ Hz; 7.65-7.35 (10H, m, aromatic-H); 7.21 and 7.14 (2H, broad, $-\text{NH}_2$); 6.19 (1H, t, H_5); 5.57 (1H, d, H_5); 5.25 (1H, t, H_2); 3.97 (1H, dd, $-\text{CH}_2\text{O}$) $J=3.9$ and 11.1 Hz; 3.87 (1H, dd, $-\text{CH}_2\text{O}$); 3.41 (1H, dd, 1H_4) $J=4.5$ and 11.7 Hz; 3.03 (1H, dd, 1H_4) $J=?$; 0.97 (9H, s, t-Bu)).

Silyether 13 (0.23 g, 0.49 mmol) was dissolved in THF (30 ml), and to it was added $n\text{-Bu}_4\text{NF}$ solution (0.50 ml, 1.0 M solution in THF, 0.50 mmol) dropwise at room temperature. The mixture was stirred for 1 hour and concentrated under vacuum. The residue was taken up with ethanol/triethylamine (2 ml/1 ml), and subjected to flash chromatography (first with EtOAc, then 20% ethanol in EtOAc) to afford a white solid 14 in 100% anomeric purity (BCH-189; 0.11 g, 0.48 mmol, 98%), which was further recrystallized from ethanol/ CHCl_3 /Hexanes mixture. (^1H NMR ($\text{DMSO}-d_6$): 7.91 (1H, d, H_6) $J=7.6$ Hz; 7.76 and 7.45 (2H, broad, $-\text{NH}_2$); 6.19 (1H, t, H_5); 5.80 (1H, d, H_5) $J=7.6$ Hz; 5.34 (1H, broad, $-\text{OH}$); 5.17 (1H, t, H_2); 3.74 (2H, m, $-\text{CH}_2\text{O}$); 3.42 (1H, dd, 1H_4) $J=5.6$ and 11.5 Hz; 3.09 (1H, dd, 1H_4) $J=4.5$ and 11.5 Hz)

BCH-189 and its analogs can also be synthesized by coupling a silylated uracil derivative with 11. Silylated uracil derivative 15 (1.80 g, 7.02 mmol) was coupled with 11 (1.72 g, 4.13 mmol) in 1,2-dichloroethane (50 ml) in the presence of SnCl_4 (5.0 ml) as described above in the the preparation of the cytosine derivative

13. The reaction was complete after 5 hours. Flash chromatography, first with 40% EtOAc in hexane and then EtOAc, afforded a white foam 16 (1.60 g, 3.43 mmol, 83%). (¹H NMR: 9.39 (1H, broad, -NH) 7.90 (1H, d, H₆) J=7.9 Hz; 7.75-7.35 (10H, m, aromatic-H); 6.33 (1H, dd, H₅); 5.51 (1H, d, H₅) J=7.9 Hz; 5.23 (1H, t, H₂); 4.11 (1H, dd, -CH₂O) J=3.2 and 11.7 Hz; 3.93 (1H, dd, -CH₂O); 3.48 (1H, dd, 1H₄) J=5.4 and 12.2 Hz; 3.13 (1H, dd, 1H₄) J=3.2 and 12.2 Hz)

10

The uracil derivative 16 can be converted to the cytosine derivative 13. The uracil derivative 16 (0.20 g, 0.43 mmol) was dissolved in a mixture of pyridine/dichloroethane (2 ml/10 ml), and the solution cooled to 0°C. Triflic anhydride (72 μl, 0.43 mmol) was added dropwise at 0°C and the mixture was warmed to room temperature and stirred for 1 hour. Additional triflic anhydride (0.50 μl, 0.30 mmol) was added and the mixture stirred for 1 hour. TLC showed no mobility with EtOAc. The reaction mixture was then decannulated into a NH₃-saturated methanol solution (30 ml) and the mixture was stirred for 12 hours at room temperature. The solution was concentrated, and the residue subjected to flash chromatography to give a tanned foam 13 (0.18 g, 0.39 mmol, 91%), which was identical with the compound obtained from the cytosine coupling reaction.

Fig. 3 illustrates the synthesis of 5-methylcytidine and thymidine derivatives of BCH-189. The acetate 11 (0.93 g, 2.23 mmol) in 1,2-dichloroethane (50 ml), was reacted with the silylated thymine derivative 17 (1.0 g, 3.70 mmol), and SnCl₄ solution (4.0 ml) in a manner similar to that described for the preparation of cytosine derivative 13. (¹H NMR: 8.10 (1H, broad, NH); 7.75-7.30 (11H, m, 10 Aromatic H's and 1H₆); 6.32 (1H, t, H₁) J=5.4 Hz; 5.25 (1H, t, H₄) J=4.2 Hz; 4.01 (1H, dd, 1H₅) J=3.9 and 11.4 Hz; 3.93 (1H, dd, 1H₅) J=4.5 and 11.4 Hz; 3.41

(1H, dd, 1H₂,) J=5.4 and 11.7 Hz; 3.04 (1H, dd, 1H₂,) J=5.7 and 11.7 Hz; 1.75 (3H, s, CH₃); 1.07 (9H, s, t-Bu))

The thymine derivative 18 (0.20 g, 0.42 mmol) was dissolved in a mixture of pyridine/dichloroethane (2 ml/10 ml), and the solution cooled to 0°C. To it was added triflic anhydride (100 µl, 0.60 mmol) dropwise at 0°C, and the mixture was allowed, with continuous stirring, to warm to room temperature. After reaching room temperature, it was stirred for 1 hour. TLC showed no mobility with EtOAc. The reaction mixture was then decannulated into the NH₃-saturated methanol solution (20 ml), and the mixture stirred for 12 hours at room temperature. The solution was concentrated, and the residue was subjected to flash chromatography to give a tanned foam 19 (0.18 g, 0.38 mmol, 90%). (¹H NMR: 7.70-7.30 (12H, m, 10 Aromatic H's, 1NH and H₆); 6.60 (1H, broad, 1NH); 6.34 (1H, t, H₁,) J=4.5 Hz; 5.25 (1H, t, H₄,) J=3.6 Hz; 4.08 (1H, dd, 1H₅,) J=3.6 and 11.4 Hz; 3.96 (1H, dd, 1H₅,) J=3.6 and 11.4 Hz; 3.52 (1H, dd, 1H₂,) J=5.4 and 12.3 Hz; 3.09 (1H, dd, 1H₂,) J=3.9 and 12.3 Hz; 1.72 (3H, s, CH₃); 1.07 (9H, s, t-Bu))

Silylether 19 (0.18 g, 0.38 mmol) was dissolved in THF (20 ml), and an n-Bu₄NF solution (0.50 ml, 1.0 M solution in THF, 0.50 mmol) was added, dropwise, at room temperature. The mixture was stirred for 1 hour and concentrated under vacuum. The residue was taken up with ethanol/triethylamine (2 ml/1 ml), and subjected to flash chromatography (first with EtOAc, then 20% ethanol in EtOAc) to afford a white solid 20 (0.09 g, 0.37 mmol, 97%), which was further recrystallized from ethanol/CHCl₃/Hexanes mixture to afford 82 mg of pure compound (89%). (¹H NMR: (in d⁶-DMSO): 7.70 (1H, s, H₆); 7.48 and 7.10 (2H, broad, NH₂); 6.19 (1H, t, H₁,) J=6.5 Hz; 5.31 (1H, t, OH); 5.16 (1H, t, 1H₄,) J=5.4 Hz; 3.72 (2H, m,

2H₅,) 3.36 (1H, dd, 1H₂,) J=6.5 and 14.0 Hz; 3.05 (1H, dd, 1H₂,) J=6.5 and 14.0 Hz; 1.85 (3H, s, CH₃))

Silylether 18 (0.70 g, 1.46 mmol) was dissolved
5 in THF (50 ml), and an n-Bu₄NF solution (2 ml, 1.0 M
solution in THF, 2 mmol) was added, dropwise, at room
temperature. The mixture was stirred for 1 hour and
concentrated under vacuum. The residue was taken up with
ethanol/triethylamine (2 ml/1 ml), and subjected to flash
10 chromatography to afford a white solid 21 (0.33 g, 1.35
mmol, 92%). (¹H NMR: (in d⁶-Acetone): 9.98 (1H, broad,
NH); 7.76 (1H, d, H₆) J=1.2 Hz; 6.25 (1H, t, H₄,) J=5.7 Hz;
5.24 (1H, t, H₁,) J=4.2 Hz; 4.39 (1H, t, OH) J=5.7 Hz; 3.85
(1H, dd, 2H₅,) J=4.2 and 5.7 Hz; 3.41 (1H, dd, 1H₂,) J=5.7
15 and 12.0 Hz; 3.19 (1H, dd, 1H₂,) J=5.4 and 12.0 Hz; 1.80
(3H, s, CH₃))

Fig. 4 illustrates the synthesis of
enantiomerically-enriched BCH-189 and its analogs. Allyl
20 butyrate 22 (19.0 g, 148 mmol) was dissolved in CH₂Cl₂ (400
ml), and ozonized at -78°C. Upon completion of
ozonolysis, dimethyl sulfide (20 ml, 270 mmol, 1.8 eq) was
added at -78°C and the mixture was warmed to room
temperature and stirred overnight. The solution was
25 washed with water (100 ml x 2), dried over MgSO₄, filtered,
concentrated, and distilled under vacuum (70-80°C at 0.5-
0.6 mm Hg) to give a colorless liquid 23 (17.0 g, 131
mmol, 88%). (¹H NMR: 9.59 (1H, s, H-CO); 4.66 (2H, s,
-CH₂O); 2.42 (2H, t, CH₂CO) J=7.2 Hz; 1.71 (2H, sex, -CH₂);
30 0.97 (3H, t, CH₃) J=7.2 Hz) (IR (neat): 2990, 2960, 2900,
1750, 1740, 1460, 1420, 1390, 1280, 1190, 1110, 1060,
1020, 990, 880, 800, 760)

Butyryloxyacetaldehyde 23 (15.0 g, 115 mmol) was
35 dissolved in toluene (200 ml) and mixed with thioglycolic
acid (8.0 ml, 115 mmol). The solution was refluxed for 5
hours while the resulting water was removed with a Dean-

Stark trap. The solution was cooled to room temperature and was transferred to a 500 ml separatory funnel. The solution was then washed with saturated NaHCO₃ solution. These aqueous washing were extracted with diethyl ether (200 ml x 2) to recuperate any crude product from the aqueous layer. The ether extracts were added to the toluene layer and the resulting mixture was washed with water (100 ml x 2), dried over MgSO₄, filtered, concentrated, and distilled under vacuum (70-80°C at 0.5-0.6 mm Hg) to give a colorless oil 24 (19 g, 93 mmol, 81%). (¹H NMR: 5.65 (1H, dd, H₅) J=5.0 and 1.4 Hz; 4.35 (1H, dd, -CH₂O) J=3.2 and 12.2 Hz; 4.29 (1H, dd, -CH₂O) J=5.7 and 12.2 Hz; 3.72 (1H, d, -CH₂S) J=16.2 Hz; 3.64 (1H, d, -CH₂S; 2.34 (2H, t, -CH₂CO) J=7.2 Hz; 1.66 (2H, sex, -CH₂); 0.95 (3H, t, CH₃) J=7.2 Hz) (IR (neat): 2980, 2960, 2900, 1780, 1740, 1460, 1410, 1390, 1350, 1300, 1290, 1260, 1220, 1170, 1110, 1080, 1070, 1000, 950, 910, 830, 820, 800, 760).

Pig liver esterase solution (90 μl) was added to a buffer solution (pH 7, 100 ml) at room temperature, and the mixture stirred vigorously for 5 minutes. The butyrate 24 (2.8 g, 13.7 mmol) was added, all at once, to the esterase/buffer solution and the mixture was stirred vigorously at room temperature for 2 hours. The reaction mixture was poured into a separatory funnel. The reaction flask was washed with ether (10 ml) and the washing was combined with the reaction mixture in the funnel. The combined mixture was extracted with hexanes three times (100 ml x 3). The three hexane extracts were combined and dried over MgSO₄, filtered, and concentrated to give the optically active butyrate 24 (1.12 g, 5.48 mmol, 40%). Enantiomeric excess was determined by an NMR experiment using a Tris[3-heptafluoropropyl-hydroxymethylene)-(+) - camphorato] europium (III) derivative as a chemical shift reagent; this procedure showed approximately 40% enrichment for one enantiomer. The remaining aqueous

layer from the reaction was subjected to a continuous extraction with CH_2Cl_2 for 20 hours. The organic layer was removed from the extraction apparatus, dried over MgSO_4 , filtered, and concentrated to give an oil (1.24 g), which
5 was shown by NMR analysis to consist of predominately the 2-hydroxymethyl-5-oxo-1,3-oxathiolane 25 with small amounts of butyric acid and the butyrate 24.

The lactone 25 (0.85 g, 4.16 mmol) was dissolved
10 in toluene (30 ml), and the solution cooled to -78°C . Dibal-H solution (9 ml, 1.0 M in hexanes, 9 mmol) was added dropwise, while the inside temperature was kept below -70°C throughout the addition. After the addition was completed, the mixture was stirred for 0.5 hours at
15 -78°C . Acetic anhydride (5 ml, 53 mmol) was added and the mixture, with continuous stirring, was allowed to reach room temperature overnight. Water (5 ml) was added to the reaction mixture and the resultant mixture was stirred for 1 hour. MgSO_4 (40 g) was then added and the mixture was
20 stirred vigorously for 1 hour at room temperature. The mixture was filtered, concentrated, and the residue flash chromatographed with 20% EtOAc in hexanes to give a colorless liquid 26 (0.41 g, 1.86 mmol, 45%) which was a mixture of anomers at the C-4 position.

25 The 2-Acetoxyethyl-5-acetoxy-1,3-oxathiolane 26 (0.40 g, 1.82 mmol) was dissolved in 1,2-dichloroethane (40 ml), and to it the silylated cytosine 12 (0.70 g, 2.74 mmol) was added, all at once, at room temperature. The
30 mixture was stirred for 10 minutes, and to it a SnCl_4 solution (3.0 ml, 1.0 M solution in CH_2Cl_2 , 3.0 mmol) was added, dropwise, at room temperature. Additional SnCl_4 solution (1.0 ml) was added after 1 hour. The reaction was followed by TLC. Upon completion of the coupling, the
35 solution was concentrated, the residue was triturated with triethylamine (2 ml) and subjected to flash chromatography (first with neat EtOAc then 20% ethanol in EtOAc) to give

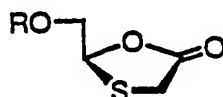
a tan solid 27 (0.42 g, 1.55 mmol, 86%). (¹H NMR: 7.73 (1H, d, H₆) J=7.5 Hz; 6.33 (1H, t, H₄) J=4.8 Hz; 5.80 (1H, d, H₅) J=7.5 Hz; 4.52 (1H, dd, 1H₅) J=5.7 and 12.3 Hz; 4.37 (1H, dd, 1H₅) J=3.3 and 12.3 Hz; 3.54 (1H, dd, H₂) J=5.4 and 12.0 Hz; 3.10 (1H, dd, 1H₃); 2.11 (3H, s, CH₃))

- The 5'-Acetate of BCH-189 27 (140 mg, 0.52 mmol) was dissolved in anhydrous methanol (10 ml), and to it was added sodium methoxide (110 mg, 2.0 mmol) in one portion.
- 10 The mixture was stirred at room temperature until the hydrolysis was complete. The hydrolysis took about 1 hour, and the reaction was followed by TLC. Upon completion, the mixture was then concentrated, and the residue taken up with ethanol (2 ml). The ethanol
- 15 solution was subjected to column chromatography using ethyl acetate first, then 20% ethanol in EtOAc to afford a white foam (110 mg, 92%), which exhibited an NMR spectrum identical to that of authentic BCH-189, 14.

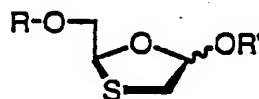
WHAT IS CLAIMED IS:

1. A method of preparing the β -isomer of an antiviral nucleoside analog comprising the steps of:

5 (a) reducing a lactone having the formula:



10 wherein R is a protecting group, to form a carboxylate, said carboxylate having the formula:



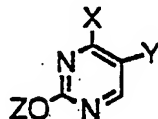
15 wherein R' is an acyl group;

20 (b) coupling said carboxylate with a silylated pyrimidine base in the presence of an effective amount of SnCl_4 to form the β -isomer of a 5' substituted 2',3'-dideoxy-3'-thia- nucleoside; and

(c) replacing said protecting group from the
25 5' position of said nucleoside with a hydrogen to form said antiviral nucleoside analog.

2. The method of Claim 1, wherein said protecting group is selected from the group consisting essentially of
30 alkyl, silyl, and acyl.

3. The method of Claim 1, wherein said silylated pyrimidine base has the formula:



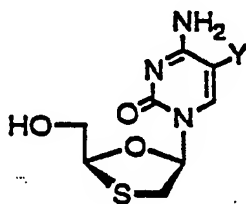
wherein X is selected from the group consisting essentially of trialkylsilyloxy and trialkylsilylamino;

10 wherein Y is selected from the group consisting essentially of hydrogen, methyl, halo, alkyl, alkenyl, alkynyl, hydroxyalkyl, carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and selenoaryl; and

15 wherein Z is a trialkylsilyl group.

4. The method of Claim 1, wherein said antiviral nucleoside analog is BCH-189.

20 5. The method of Claim 1, wherein said antiviral nucleoside analog comprises the formula:

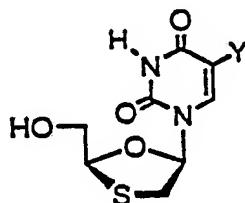


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wherein Y is selected from the group consisting essentially of halo, alkyl, alkenyl, alkynyl, hydroxyalkyl, carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and

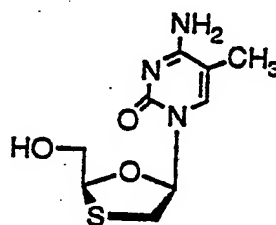
35 selenoaryl.

6. The method of Claim 1, wherein said antiviral nucleoside analog comprises the formula:

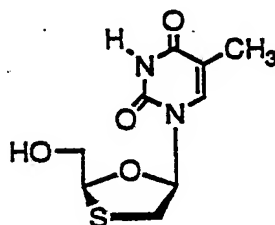


10 wherein Y is selected from the group consisting essentially of hydrogen, halo, alkyl, alkenyl, alkynyl, hydroxyalkyl, carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and selenoaryl.

15 7. The method of Claim 1, wherein said antiviral nucleoside analog comprises the formula:



25 8. The method of Claim 1, wherein said antiviral nucleoside analog comprises the formula:



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9. The method of Claim 1, further comprising the steps prior to (a) of:

(1) ozonizing a compound having the formula $\text{CH}_2\text{CHCH}_2\text{OR}$ to form a glycoaldehyde having the formula OHCCH_2OR , wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and

(2) adding an effective amount of thioglycolic acid to said glycoaldehyde to form said lactone.

10. The method of Claim 1, wherein said reduction of said lactone is accomplished by addition of a reducing agent followed by addition of an effective amount of a carboxylic anhydride.

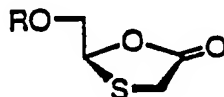
11. The method of Claim 10, wherein said reducing agent is selected from the group consisting essentially of DIBAL-H, RED-AL, and NaBH_4 .

12. The method of Claim 1, wherein said replacement of said protecting group is accomplished by addition of an effective amount of $(n\text{-C}_4\text{H}_9)_4\text{NF}$.

13. The method of Claim 1, wherein said replacement of said protecting group is accomplished by addition of an effective amount of sodium methoxide.

14. A method of preparing an enantiomerically-enriched β -isomer of an antiviral nucleoside analog comprising the steps of:

(a) adding an effective amount of a stereoselective enzyme to a lactone having the formula:



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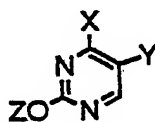
wherein R is an acyl protecting group, to form enantiomerically-enriched 2-hydroxymethyl-5-oxo-1,3-oxathialane;

(b) reducing said enantiomerically-enriched 2-hydroxymethyl-5-oxo-1,3-oxathiolane to form an enantiomerically-enriched 2-acyloxymethyl-5-acyloxy-1,3-oxathiolane;

(c) coupling said enantiomerically-enriched 2-acyloxymethyl-5-acyloxy-1,3-oxathiolane with a silylated pyrimidine base in the presence of an effective amount of SnCl_4 to form the β -isomer of a 2',3'-dideoxy-5'-acyloxymethyl-3'-thia-nucleoside; and

(d) replacing the 5'-acyloxymethyl substituent of said nucleoside with a hydroxymethyl substituent to form said antiviral nucleoside analog.

15. The method of Claim 14, wherein said silylated pyrimidine base has the formula:



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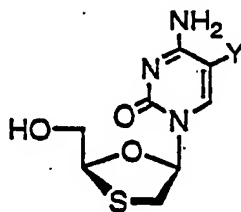
wherein X is selected from the group consisting essentially of trialkylsilyloxy and trialkylsilylamino;

wherein Y is selected from the group consisting essentially of hydrogen, methyl, halo, alkyl, alkenyl, alkynyl, hydroxyalkyl, carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and selenoaryl; and

wherein Z is a trialkylsilyl group.

16. The method of Claim 14, wherein said antiviral nucleoside analog is BCH-189.

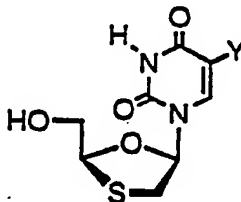
17. The method of Claim 14, wherein said antiviral nucleoside analog comprises the formula:



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wherein Y is selected from the group consisting essentially of halo, alkyl, alkenyl, alkynyl, hydroxyalkyl, carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and
15 selenoaryl.

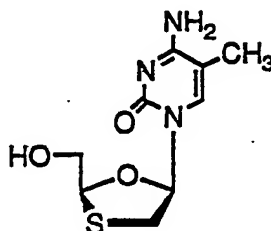
18. The method of Claim 14, wherein said antiviral nucleoside analog comprises the formula:



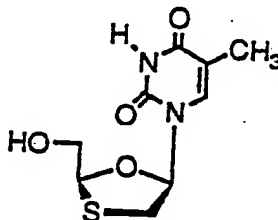
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wherein Y is selected from the group consisting essentially of hydrogen, halo, alkyl, alkenyl, alkynyl, hydroxyalkyl, carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and
30 selenoaryl.

19. The method of Claim 14, wherein said antiviral nucleoside analog comprises the formula:



20. The method of Claim 14, wherein said antiviral nucleoside analog comprises the formula:



21. The method of Claim 14, further comprising the steps prior to (a) of:

(1) ozonizing a compound having the formula $\text{CH}_2\text{CHCH}_2\text{OR}$ to form a glycoaldehyde having the formula OHCCH_2OR , wherein R is an acyl group; and

25 (2) adding an effective amount of thioglycolic acid to said glycoaldehyde to form said lactone.

22. The method of Claim 14, wherein said reduction of said lactone is accomplished by addition of a reducing agent followed by addition of an effective amount of a carboxylic anhydride.

23. The method of Claim 22, wherein said reducing agent is selected from the group consisting essentially of
35 DIBAL-H, RED-AL, and NaBH_4 .

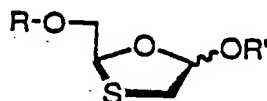
24. The method of Claim 14, wherein said stereoselective enzyme is selected from the group consisting of pig liver esterase, porcine pancreatic lipase, and subtilisin.

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25. The method of Claim 14, wherein said replacement of said protecting group is accomplished by addition of an effective amount of sodium methoxide.

10 26. A method of preparing a carboxylate having the formula:

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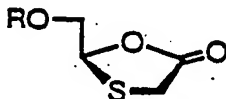
wherein R is a protecting group; and
wherein R' is an acyl group, comprising the

20 steps of:

(a) ozonizing a compound having the formula $\text{CH}_2\text{CHCH}_2\text{OR}$ to form a glycoaldehyde having the formula OHCCH_2OR , wherein R is a protecting group;

(b) adding an effective amount of thioglycolic
25 acid to said glycoaldehyde to form a lactone having the formula:

30



; and

(c) reducing said lactone to form said
35 carboxylate.

27. The method of Claim 26, wherein said reduction of said lactone is accomplished by a addition of a reducing agent followed by addition of an effective amount of a carboxylic anhydride.

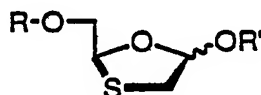
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28. The method of Claim 26, wherein said reducing agent is selected from the group consisting essentially of DIBAL-H, RED-AL, and NaBH_4 .

10 29. The method of Claim 26, wherein said protecting group is selected from the group consisting essentially of alkyl, silyl, and acyl.

30. A carboxylate having the formula:

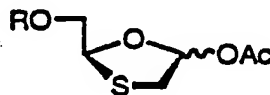
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20 wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and wherein R' is an acyl group.

31. An acetate having the formula:

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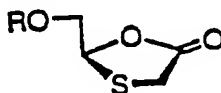
wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl.

32. A method of preparing enantiomerically-enriched
35 2-acyloxymethyl-5-acyloxy-1,3-oxathiolane comprising the steps of:

(a) ozonizing a compound having the formula $\text{CH}_2\text{CHCH}_2\text{OR}$ to form a glycoaldehyde having the formula OHCCH_2OR , wherein R is a protecting group;

(b) adding an effective amount of thioglycolic acid to said glycoaldehyde to form a lactone having the formula:

10



; and

(c) adding an effective amount of a stereoselective enzyme to said lactone to form enantiomerically-enriched 2-hydroxymethyl-5-oxo-1,3-oxathialane; and

(d) reducing said enantiomerically-enriched 2-hydroxymethyl-5-oxo-1,3-oxathiolane to form enantiomerically-enriched 2-acyloxymethyl-5-acyloxy-1,3-oxathiolane.

33. The method of Claim 32, wherein said reduction of said enantiomerically-enriched 2-butyryloxymethyl-5-oxo-1,3-oxathiolane is accomplished by a addition of a reducing agent followed by addition of an effective amount of a carboxylic anhydride.

34. The method of Claim 32, wherein said reducing agent is selected from the group consisting essentially of DIBAL-H, RED-AL, and NaBH_4 .

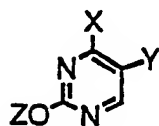
35. The method of Claim 32, wherein said stereoselective enzyme is selected from the group consisting of pig liver esterase, porcine pancreatic lipase, and subtilisin.

36. The method of Claim 32, wherein said protecting group is selected from the group consisting essentially of alkyl, silyl, and acyl.
- 5 37. Enantiomerically-enriched 2-hydroxymethyl-5-oxo-1,3-oxathiolane.
38. Enantiomerically-enriched 2-acyloxymethyl-5-acyloxy-1,3-oxathiolane.
- 10 39. Enantiomerically-enriched 2-acetoxymethyl-5-acetoxy-1,3-oxathiolane.
40. A method of preparing the β -isomer of a
15 substituted nucleoside comprising the step coupling a carboxylate having the formula:



- wherein R is a protecting group; and
- 25 wherein R' is an acyl group, with a silylated pyrimidine base in the presence of an effective amount of SnCl_4 to form the β -isomer of a 5' substituted 2',3'-dideoxy-3'-thia- nucleoside.
- 30 41. The method of Claim 40, wherein said protecting group is selected from the group consisting essentially of alkyl, silyl, and acyl.

42. The method of Claim 40, wherein said silyated pyrimidine base has the formula:



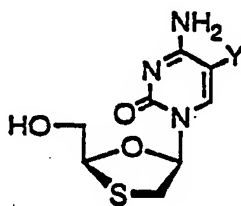
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wherein X is selected from the group consisting essentially of trialkylsilyloxy and trialkylsilylamino;

wherein Y is selected from the group consisting essentially of hydrogen, methyl, halo, alkyl, alkenyl, alkynyl, hydroxyalkyl, carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and selenoaryl; and

wherein Z is a trialkylsilyl group.

20 43. A substituted nucleoside having the formula:



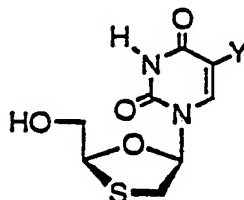
wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and

30 wherein Y is selected from the group consisting essentially of alkyl, alkenyl, alkynyl, hydroxyalkyl, carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and selenoaryl.

35

44. A substituted nucleoside having the formula:

5



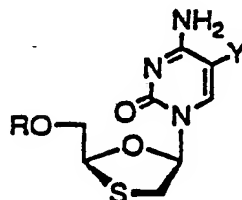
- wherein R is selected from the group consisting
10 essentially of alkyl, silyl, and acyl; and

wherein Y is selected from the group consisting
essentially of alkyl, alkenyl, alkynyl, hydroxyalkyl,
carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl,
cycloalkenyl, thioaryl, and selenoaryl.

15

45. A substituted nucleoside having the formula:

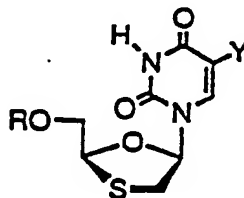
20



- wherein R is selected from the group consisting
25 essentially of alkyl, silyl, and acyl; and
wherein Y is a hydrogen.

46. A substituted nucleoside having the formula:

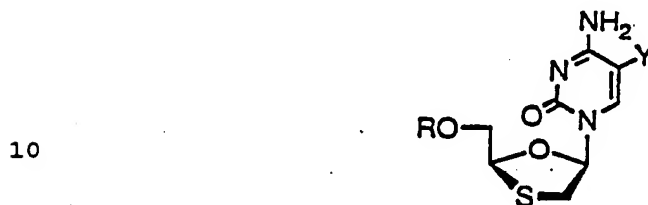
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35

wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and wherein Y is a hydrogen.

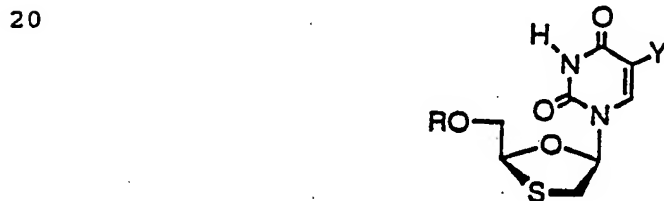
- 5 47. A substituted nucleoside having the formula:



wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and

- 15 wherein Y is selected from the group consisting of chloro, bromo, fluoro, and iodo.

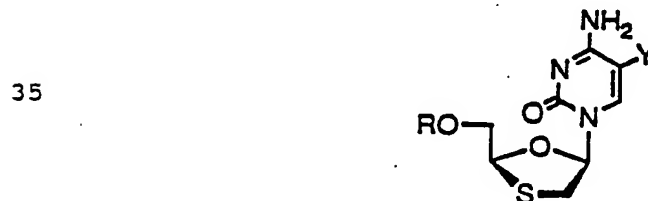
48. A substituted nucleoside having the formula:



25 wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and

wherein Y is selected from the group consisting of chloro, bromo, fluoro, and iodo.

- 30 49. A substituted nucleoside having the formula:

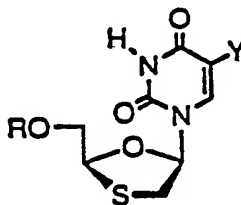


wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and wherein Y is a methyl group.

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50. A substituted nucleoside having the formula:

10

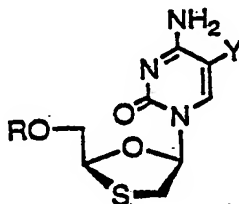


15

wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and wherein Y is a methyl group.

51. An enantiomerically-enriched substituted
20 nucleoside having the formula:

25

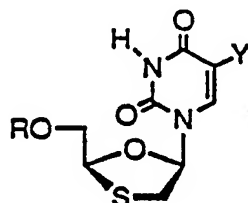


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wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and wherein Y is selected from the group consisting essentially of alkyl, alkenyl, alkynyl, hydroxyalkyl, carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and selenoaryl.

35

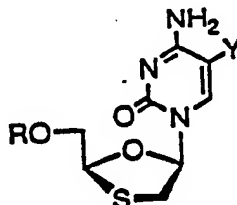
52. An enantiomerically-enriched substituted nucleoside having the formula:



10 wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and

wherein Y is selected from the group consisting essentially of alkyl, alkenyl, alkynyl, hydroxyalkyl, carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, 15 cycloalkenyl, thioaryl, and selenoaryl.

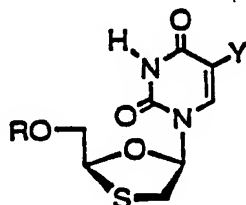
53. An enantiomerically-enriched substituted nucleoside having the formula:



25 wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and

wherein Y is a hydrogen.

30 54. An enantiomerically-enriched substituted nucleoside having the formula:

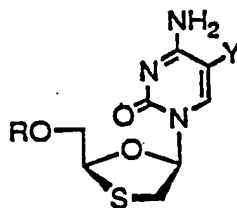


wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and
wherein Y is a hydrogen.

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55. An enantiomerically-enriched substituted nucleoside having the formula:

10



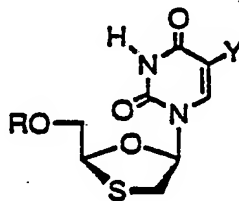
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wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and
wherein Y is selected from the group consisting essentially of chloro, bromo, fluoro, and iodo.

20

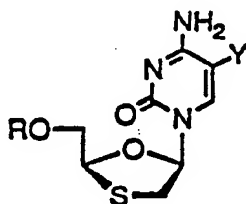
56. An enantiomerically-enriched substituted nucleoside having the formula:

25



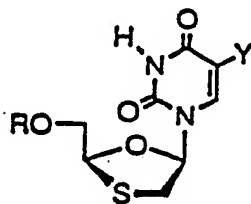
wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and
wherein Y is selected from the group consisting essentially of chloro, bromo, fluoro, and iodo.

57. An enantiomerically-enriched substituted nucleoside having the formula:



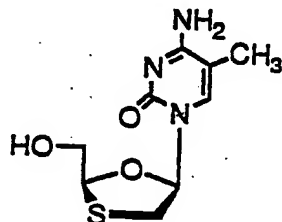
wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and wherein Y is a methyl group.

15 58. An enantiomerically-enriched substituted nucleoside having the formula:



wherein R is selected from the group consisting essentially of alkyl, silyl, and acyl; and wherein Y is a methyl group.

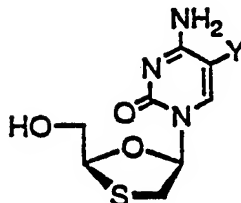
59. A compound of the formula:



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60. A compound of the formula:

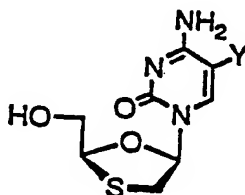
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wherein Y is selected from the group consisting
10 of chloro, bromo, fluoro, and iodo.

61. A compound of the formula:

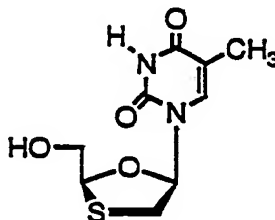
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20 wherein Y is selected from the group consisting
essentially of alkyl, alkenyl, alkynyl, hydroxyalkyl,
carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl,
cycloalkenyl, thioaryl, and selenoaryl.

25 62. A compound of the formula:

30

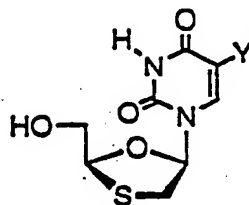


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63. A compound of the formula:

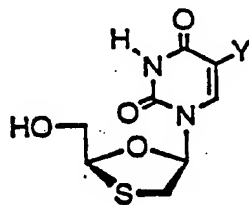
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wherein Y is selected from the group consisting
10 of chloro, bromo, fluoro, and iodo.

64. A compound of the formula:

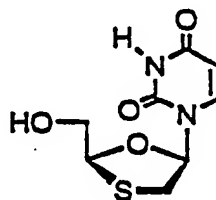
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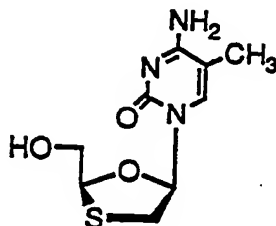
20 wherein Y is selected from the group consisting
essentially of alkyl, alkenyl, alkynyl, hydroxyalkyl,
carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl,
cycloalkenyl, thioaryl, and selenoaryl.

25 65. A compound of the formula:

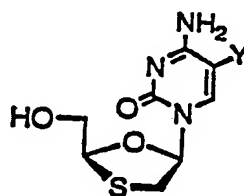
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66. An enantiomerically-enriched compound of the formula:

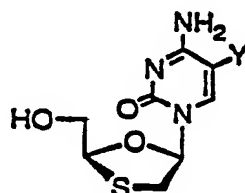


67. An enantiomerically-enriched compound of the formula:



wherein Y is selected from the group consisting of chloro, bromo, fluoro, and iodo.

68. An enantiomerically-enriched compound of the formula:

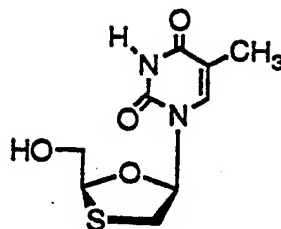


wherein Y is selected from the group consisting essentially of alkyl, alkenyl, alkynyl, hydroxyalkyl, carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and selenoaryl.

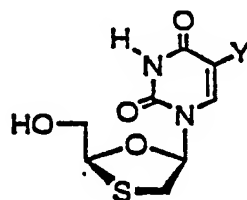
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69. An enantiomerically-enriched compound of the formula:

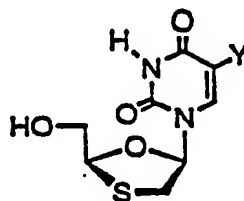


70. An enantiomerically-enriched compound of the formula:



20 wherein Y is selected from the group consisting of chloro, bromo, fluoro, and iodo.

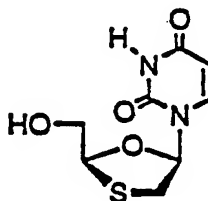
71. An enantiomerically-enriched compound of the formula:



30 wherein Y is selected from the group consisting essentially of alkyl, alkenyl, alkynyl, hydroxyalkyl, carboxyalkyl, thioalkyl, selenoalkyl, phenyl, cycloalkyl, cycloalkenyl, thioaryl, and selenoaryl.

72. An enantiomerically-enriched compound of the formula:

5



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Figure 1

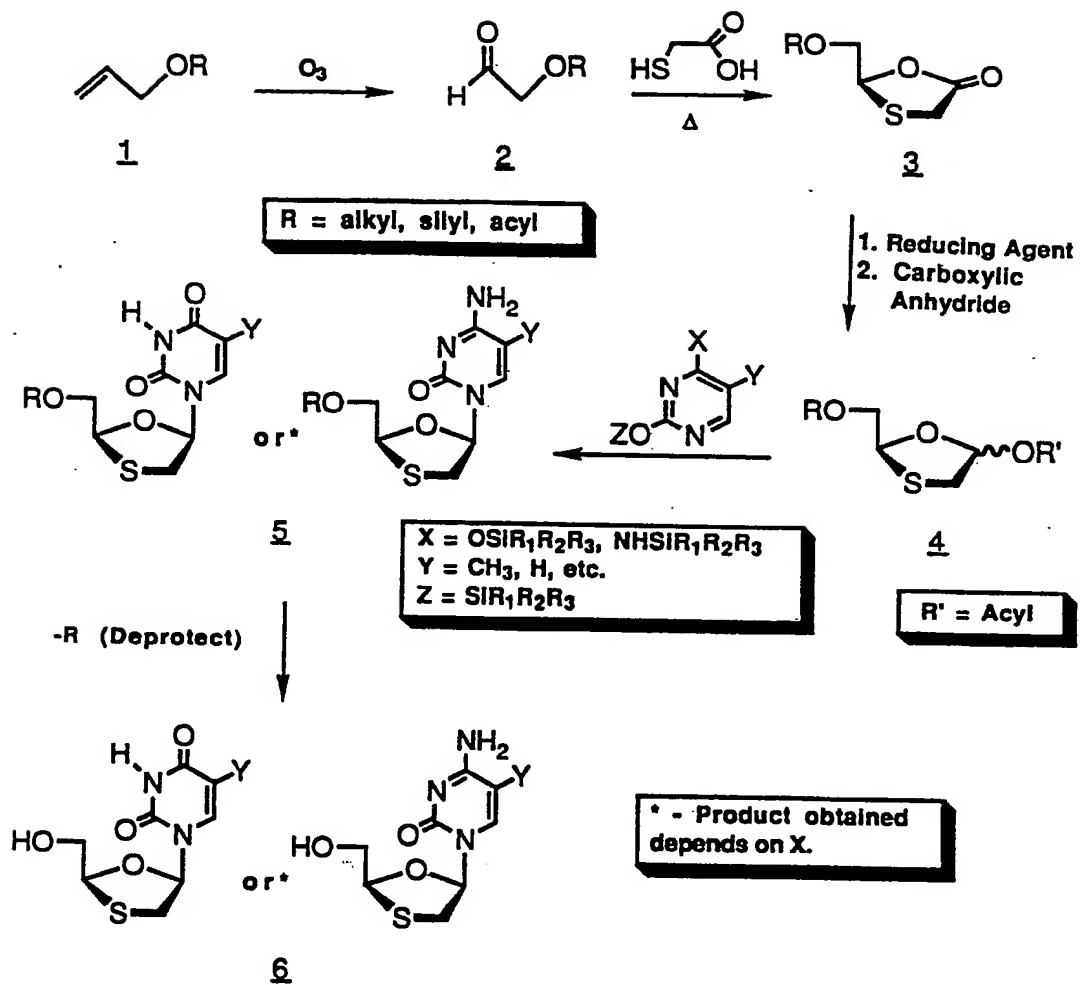


Figure 2

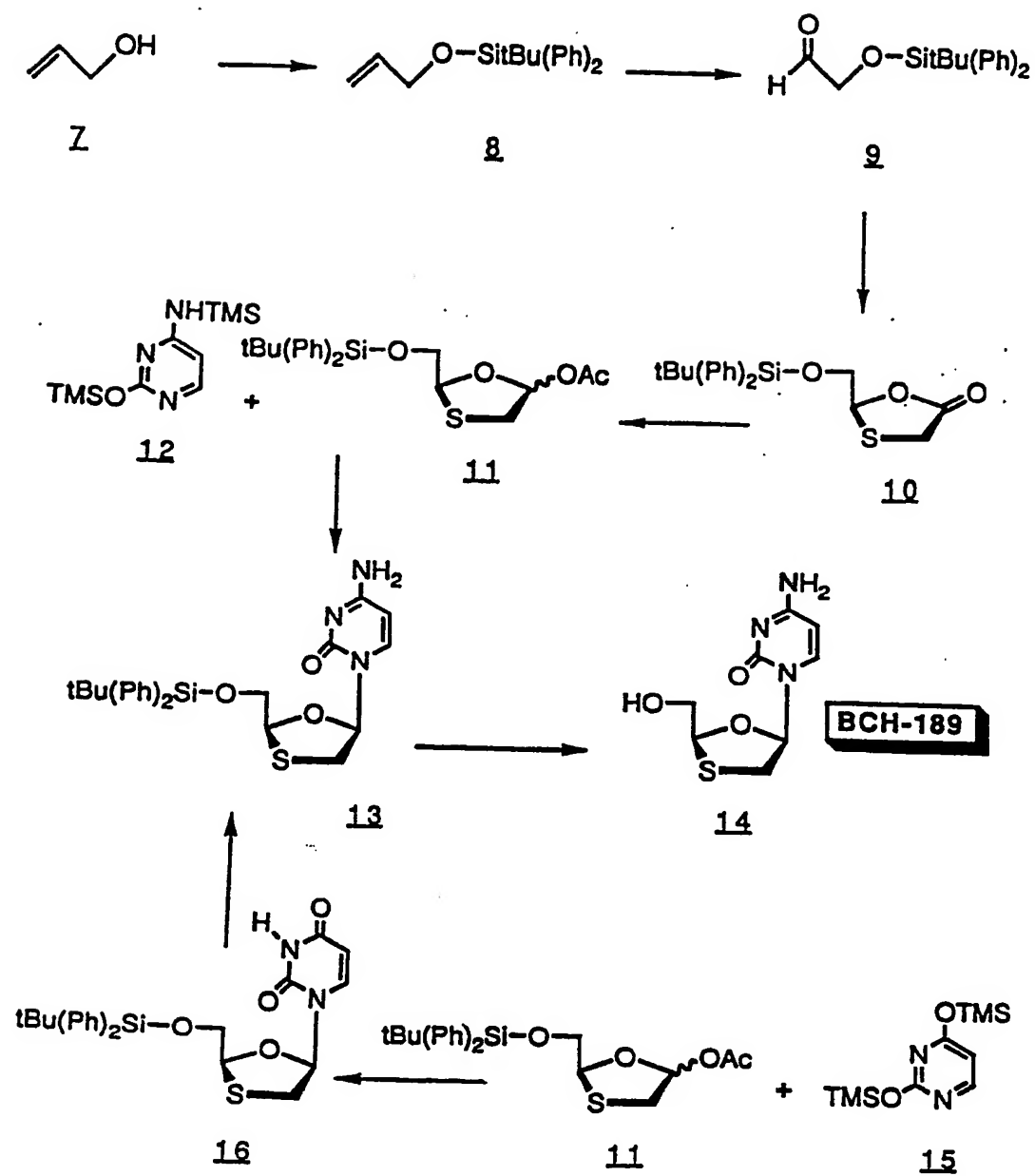
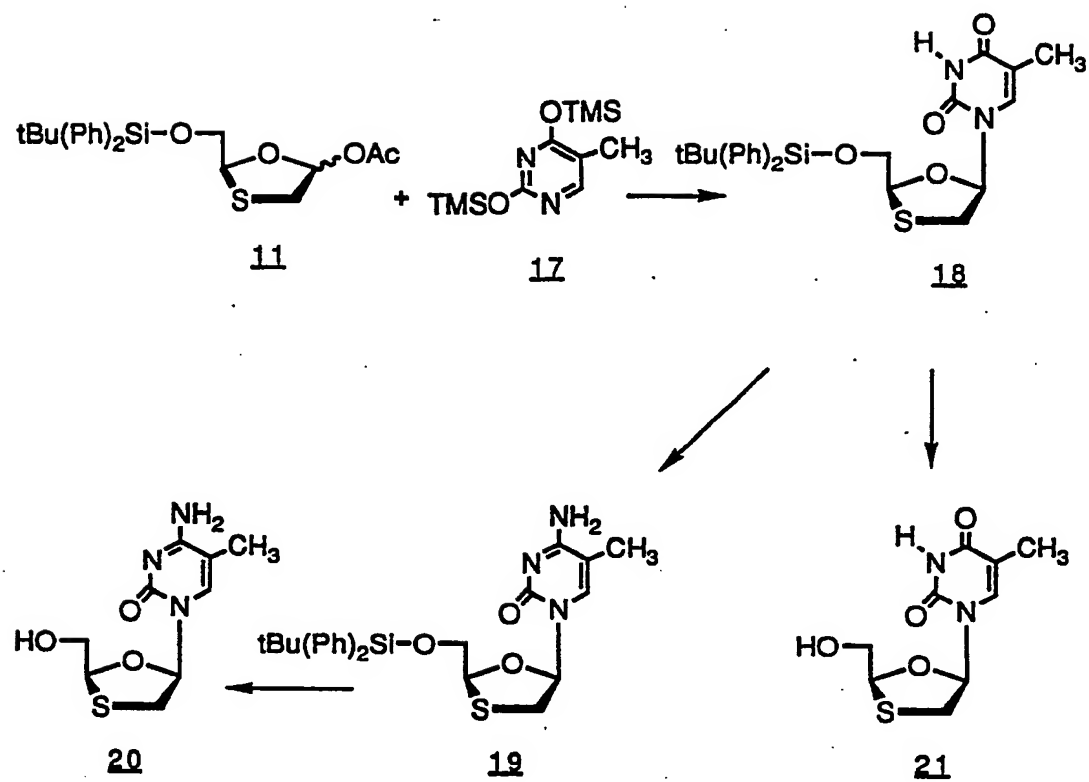
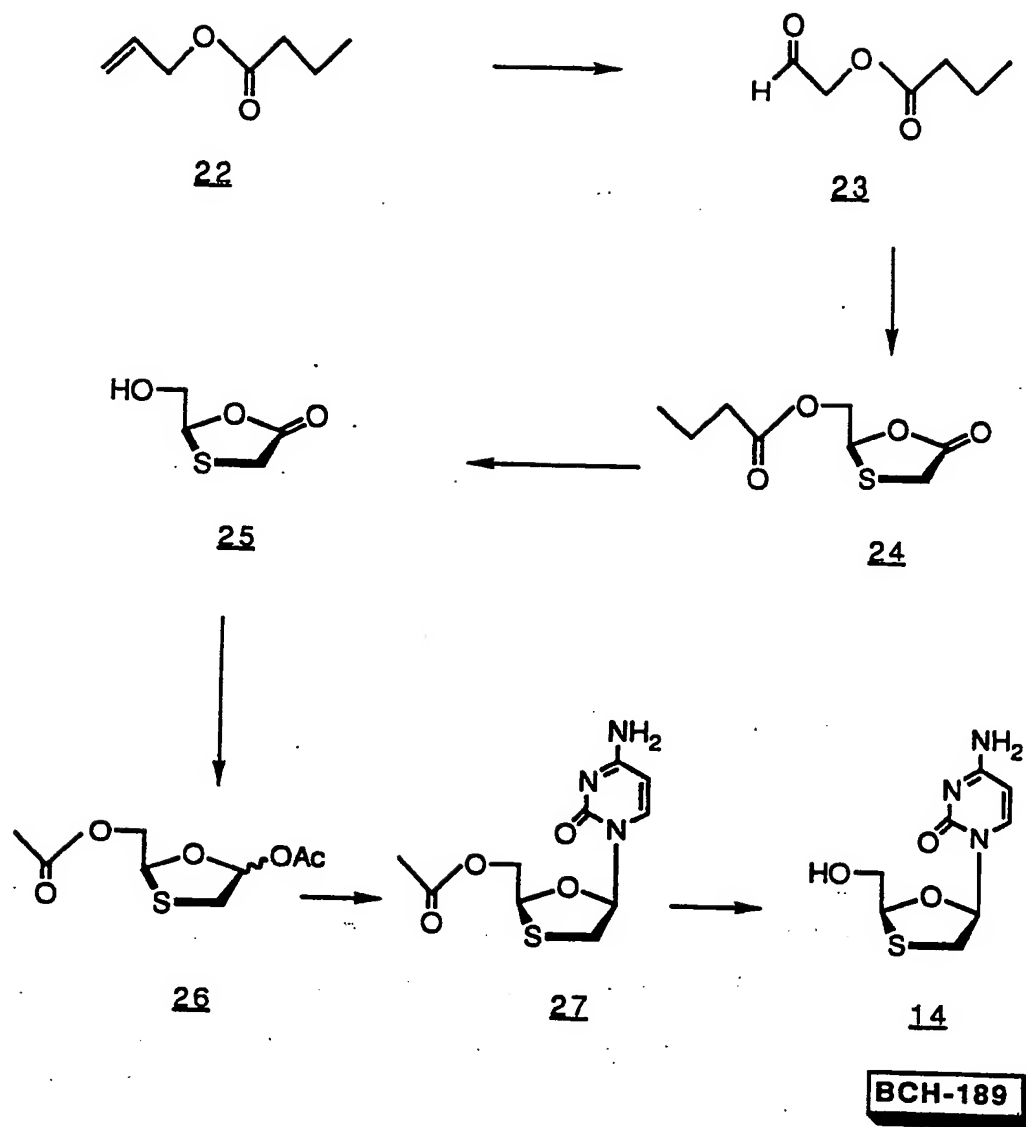


Figure 3




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Figure 4



INTERNATIONAL SEARCH REPORT

International Application No. **PCT/US91/00685**

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ¹		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC(5): A61K 31/505; C07D 239/02, 411/04		
US CL 514/269,274; 544/229,310,313,314,317; 549/30		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System ³	Classification Symbols	
US	514/269,274; 544/229,310,313,314,317; 549/30	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category ⁶	Citation of Document, ¹⁵ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁶
A	US, 4,000,137 (American Home Products Corporation) 28 December 1976, see entire document.	1-72
A	US, 4,336,381 (Shinogi & Co. Ltd.) 22 June 1982, see entire document.	1-72
A	US, 4,415,573 (Chugai Seiyaku Kabushiki Kaisha) 15 November 1983.	1-72
A	WO 85/00608 (Teijin Ltd.) 14 February 1985, see entire document.	1-72
A	JP, A, 52/059,171 (Asahi Chemical IND KK) 16 May 1977, see entire document.	1-72
A	JP, A, 53/021,178 (Kojin KK) 27 February 1978, see entire document.	1-72
A	EP, A, 46,307 (Chugai Seiyaku KK) 24 February 1982, see entire document.	1-72
A	JP, A, 58/039,672 (Chugai Pharmaceutical KK) 08 March 1983, see entire document.	1-72
<p>[*] Special categories of cited documents: ¹³</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search ¹	Date of Mailing of this International Search Report ¹	
21 April 1991	13 JUN 1991	
International Searching Authority ¹	Signature of Authorized Officer ¹⁸	
ISA/US	 NGUYEN NGOC-HO Cecilia Shen INTERNATIONAL DIVISION	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	Tetrahedron Letters, vol. 30, No. 46, 1989. D.W. Norbeck et al. "A new 2'-3'-Dideoxynucleoside Prototype with in vitro activity against HIV".	1-72
A	Journal of Medicinal Chemistry, 1987, 30, 1270-1278. Piet Herdewijn, et al. 3'-Substituted 2',3'-Dideo- xynucleoside Analogues as Potential Anti-HIV (HTLV- III/LAV) Agents. See entire document.	1-72
A	Journal of Medicinal Chemistry, 1987, 30, H40-444. Tai- Shun Lin et al. "Synthesis and Antiviral Activity- of Various 3'-Azido, 3'-Amino, 2'3'-Unsaturated, and 2'3'-Dideoxy Analogues of Pyrimidine Deoxyribonucleo- sides against Retroviruses". see entire document.	1-72

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed require-
ments to such an extent that no meaningful international search can be carried out², specifically:

3. ☐ Claim numbers because they are dependent claims not drafted in accordance with the second and third sentences of
PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING³

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only
those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to
the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not
invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.